


# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HP/6243448		<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/GB2004/003365		International filing date (day/month/year) 04.08.2004		Priority date (day/month/year) 04.08.2003
International Patent Classification (IPC) or national classification and IPC A01N1/02, A61K31/416, A61K31/69, A61K45/06, A61P7/04, A61P9/04, A61P9/10, A61P9/12, A61P11/00, A61P29/00, A61P31/00, A61P35/00, A61P41/00				
Applicant NORTHWICK PARK INSTITUTE FOR MEDICAL RESEARCH				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 11 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 9 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  06.06.2005		Date of completion of this report  11.11.2005		
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer  Albrecht, S  Telephone No. +49 89 2399-7864		



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AP20 Rec'd PCT/PTO 03 FEB 2006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-30 as originally filed

Claims, Numbers

1-57 received on 07.06.2005 with letter of 06.06.2005

Drawings, Sheets

1/11-11/11 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☒ the claims, Nos. 58,59
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-34,45-52

because:

☒ the said international application, or the said claims Nos. 18-34,45-52 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-34,46-48,50-52 (all in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	5-16,22-33,35-57
	No: Claims	1-4,17-21,34
Inventive step (IS)	Yes: Claims	5-12,22-29,36,41,54
	No: Claims	1-4,13-21,30-35,37-40,42-53,55-57
Industrial applicability (IA)	Yes: Claims	1-17,35-44,53-57
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

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**Re Item III****Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

III.1. Claims 18-34, 45-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.2. The attention of the applicant is drawn to the fact that for the present application only an incomplete search has been carried out with respect to claims 1-34, 46-48, 50-52, the reasons being as follows:

Claims 1-34, 46-48, 50-52 are directed to a method of treatment, as they encompass the administration of active agents to patients. However, the intended purpose is partially defined by reference to a desirable characteristic or property, namely "for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO". Such is not a method of therapy according to R.67.1(iv) PCT as the intended disease(s), disorder(s) or dysfunction(s) to be treated is/are not defined. Claims 1-36, 48-50, 52-54 cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for a limited number of such methods. Accordingly, since a meaningful search over the whole of the claimed scope is impossible, the search has thus been restricted to the diseases explicitly listed in claims 1-3, 19-21, 48-51. With respect to examination, the feature "for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent" will not be taken into consideration for the assessment of novelty and inventive step of claims 1-34, 46-48, 50-52 in view of the fact that it fails to comply with the requirements of Article 6 PCT as mentioned above.

**Re Item V****Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents (D1-D8) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR). The cited passage(s) for each citation will

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be considered unless otherwise specified.

**V.1. Novelty (claims 1-34, 46-48, 50-52 under the proviso of item III.2)**

V.1.1. Claims 1-4, 17-21, 34 do not appear to be novel in the sense of Article 33 (2) PCT, the reasons being as follows:

a) D3 describes the use of boranocarbonates (see examples 18-22) for treating arteriosclerosis.

Therefore, D3 is prejudicial to the novelty of claims 1, 3, 4, 17, 18, 20, 21, 34.

b) D4 pertains to N-boronated purine and pyrimidine bases, nucleoside(s) and oligonucleotide(s) for the treatment of tumours.

Hence, D4 takes away the novelty of claims 1-4, 17-21, 34.

d) D7 reports on the protective effect of a boranocarbonate (compound 2) against septic shock (table III).

Thus, D7 anticipates the subject-matter of claims 1, 3, 4, 17, 18, 20, 21, 34.

V.1.2. Claims 5-16, 22-33, 35-57 appear to be novel over the available prior art.

**V.2. Inventive step (claims 1-34, 46-48, 50-52 under the proviso of item III.2)**

V.2.1. Claims 1-4, 17-21, 34:

Being not new, the subject-matter of present claims 1-4, 17-21, 34 cannot be considered as inventive either.

V.2.2. Claims 13-16, 30-33, 35, 37-40, 42-53, 55-57:

a) D5, which is considered to represent the most relevant state of the art, discloses the use of metal carbonyl compounds for the therapeutic delivery of carbon monoxide (CO) as well as for organ perfusion.

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b) The subject-matter of claims 13-16, 30-33, 35, 37-40, 42-53, 55-57 differs mainly from D5 in that the in D5 mentioned metal carbonyl compounds do not comprise a boron atom.

c) The technical problem to be solved by the present invention consists of providing further compositions which deliver CO to a physiological target in order to treat those diseases which respond to CO in a human/animal body (p.10) or to provide adequate perfusion of an isolated organ.

d) The solution proposed by the applicant constitutes a composition comprising a boranocarbonate.

e) Nevertheless, there is no indication supporting the fact that the technical problem can indeed be solved over the full scope of the invention, because claims 13-16, 30-33, 35, 37-40, 42-53, 55-57 do not specify that the boron atom of the claimed boranocarbonates must be adjacent to the carbonyl moiety. This is however a prerequisite for the release of CO by the claimed boranocarbonates.

Consequently, an inventive step cannot be acknowledged for present claims 13-16, 30-33, 35, 37-40, 42-53, 55-57.

V.2.3. Claims 5-12, 22-29, 36, 41, 54:

a) D5 is considered to represent the most relevant state of the art.

b) The subject-matter of claims 5-12, 22-29, 36, 41, 54 differs from D5 in that the in D5 mentioned metal carbonyl compounds do not comprise a boron atom.

c) The technical problem to be solved by the present invention consists of providing further compositions which deliver CO to a physiological target in order to treat those diseases which respond to CO in a human/animal body (p.10) or to provide adequate perfusion of an isolated organ.

d) The solution proposed by the applicant constitutes a composition comprising a boranocarbonate as defined in claims 5-12.

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e) D6 describes the use of boranocarbonates as CO source and as reducing agent in the chemical synthesis of transition metal carbonyl complexes. In particular, the CO is released upon heating an aqueous solution of the boranocarbonate (cf. p.2, I.34-35 and examples 2,3 in which the solution is heated to 75°C). Furthermore, it is specified in this document that the boranocarbonates may also be applied in other circumstances wherein a CO source in aqueous solution is required (p.7, I.10-14). Nevertheless, D6 does not contain any indication that boranocarbonates are able to release CO under physiological conditions. In addition, the applicant has provided evidence that the technical problem can be solved by the present invention.

f) Hence, claims 5-12, 22-29, 36, 41, 54 appear to involve an inventive step in the sense of Art.33(3) PCT.

### **V.3. Industrial Applicability**

For the assessment of the present claims 18-34, 45-52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

### **Re Item VI**

#### **Certain documents cited**

##### **Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO03066067	14/08/2003	03/02/2003	04/02/2002

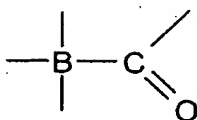
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CLAIMS

1. Use of a boranocarbonate compound or ion in the manufacture of a medicament, for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent, or for the treatment of any of acute or chronic systematic hypertension, radiation damage, endotoxic shock, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, post-operative ileus, arteriosclerosis, post-ischemic organ damage, angina, haemorrhagic shock, sepsis, penile erectile dysfunction, vascular restenosis, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis or for treatment in balloon angioplasty, aortic transplantation or survival of a transplanted organ.
2. Use according to claim 1 wherein the medicament is for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent, or for the treatment of any of acute or chronic systematic hypertension, hyperoxia-induced injury, cancer by the pro-apoptotic effect of CO, transplant rejection, post-operative ileus, post-ischemic organ damage, angina, haemorrhagic shock, penile erectile dysfunction, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis or for treatment in balloon angioplasty or aortic transplantation.
3. Use according to either claim 1 or claim 2 wherein the medicament is suitable for administration by an oral, intravenous, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal, transdermal, transmucosal or suppository route.
4. Use according to any one of claims 1 to 3 wherein the molecular structure of the boranocarbonate compound or ion includes the moiety

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5. Use according to claim 4 wherein the boranocarbonate compound or ion includes the moiety  $\text{BH}_3\text{-CO-}$ .
6. Use according to claim 4 or 5 wherein the boranocarbonate
- 5 is a compound or anion of the formula:



wherein:-

x is 1, 2 or 3

y is 1, 2 or 3

z is 0, 1 or 2

$x + y + z = 4$ ,

each Q is  $\text{O}^-$ , representing a carboxylate anionic form, or is OH, OR,  $\text{NH}_2$ , NHR,  $\text{NR}_2$ , SR or halogen, where the or each R is alkyl (preferably of 1 to 4 carbon atoms),

each Z is halogen,  $\text{NH}_2$ , NHR',  $\text{NR}'_2$ , SR' or OR' where the or each R' is alkyl (preferably of 1 to 4 carbon atoms).

7. Use according to claim 6 wherein z is 0.
8. Use according to claim 6 or 7 where y is 1.
- 10 9. Use according to claim 6 where x is 3.
10. Use according to any one of claims 6 to 9 where the boranocarbonate is an anion, with at least one Q in the form of  $\text{O}^-$  or OR, and the composition includes at least one metal cation.
- 15 11. Use according to claim 10 wherein the or each metal cation is an alkali metal cation or an alkaline earth metal cation.
12. Use according to claim 11 wherein the boranocarbonate is  $\text{Na}_2(\text{H}_3\text{BCO}_2)$ .

13. Use according to any one of claims 1 to 12 wherein the medicament further includes a guanylate cyclase stimulant or stabilizer.

14. Use according to claim 13 wherein the guanylate cyclase stimulant or stabilizer is a molecule or ion uncombined with the boranocarbonate compound or ion.

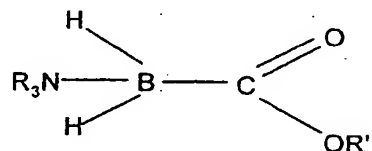
15. Use according to claim 13 or 14 wherein the guanylate cyclase stimulant or stabilizer is YC-1.

16. Use according to any one of claims 13 to 15 wherein the medicament is adapted for one of simultaneous and sequential administration of the boranocarbonate compound or ion and the guanylate cyclase stimulant or stabilizer.

17. Use according to any one of claims 1 to 16 wherein the boranocarbonate compound or ion is other than

I.  $K_2 (H_3BCOO)$

II.



where R, R' = H, alkyl, perfluoroalkyl.

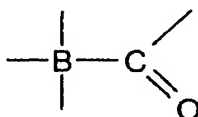
18. Method of treatment of a mammal comprising stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent, or the treatment of any of acute or chronic systemic hypertension, radiation damage, endotoxic shock, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, post-operative ileus, arteriosclerosis, post-ischemic organ damage, angina, haemorrhagic shock, sepsis, penile erectile dysfunction, vascular restenosis, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis, or treatment in balloon angioplasty, aortic transplantation or survival of a transplanted organ, by administration of a boranocarbonate

compound or ion adapted to make CO available for physiological effect.

19. Method according to claim 18 comprising stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent, or treatment of any of acute or chronic systemic hypertension, hyperoxia-induced injury, cancer by the pro-apoptotic effect of CO, transplant rejection, post-operative ileus, post-ischemic organ damage, angina, haemorrhagic shock, penile erectile dysfunction, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis, or treatment in balloon angioplasty or aortic transplantation.

20. Method according to claim 18 or claim 19 wherein including administration by an oral, intravenous, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal, transdermal, transmucosal or suppository route.

21. Method according to any one of claims 18 to 20 wherein the molecular structure of the boranocarbonate compound or ion includes the moiety



22. Method according to claim 21 wherein the boranocarbonate compound or ion includes the moiety  $\text{BH}_3\text{-CO-}$ .

23. Method according to claim 21 or 22 wherein the boranocarbonate is a compound or anion of the formula:



wherein:-

x is 1, 2 or 3

y is 1, 2 or 3

z is 0, 1 or 2

$$x + y + z = 4,$$

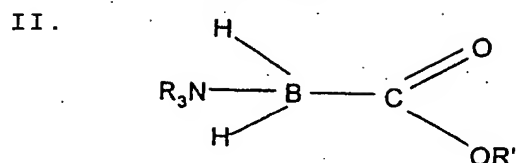
each Q is O<sup>-</sup>, representing a carboxylate anionic form, or is OH, OR, NH<sub>2</sub>, NHR, NR<sub>2</sub>, SR or halogen, where the or each R is alkyl (preferably of 1 to 4 carbon atoms),

each Z is halogen, NH<sub>2</sub>, NHR', NR'<sub>2</sub>, SR' or OR' where the or each R' is alkyl (preferably of 1 to 4 carbon atoms).

24. Method according to claim 23 wherein z is 0.
25. Method according to claim 23 or 24 where y is 1.
26. Method according to claim 23 where x is 3.
- 5 27. Method according to any one of claims 23 to 26 where the boranocarbonate is an anion, with at least one Q in the form of O<sup>-</sup> or OR, and the composition includes at least one metal cation.
28. Method according to claim 27 wherein the or each metal
- 10 cation is an alkali metal cation or an alkaline earth metal cation.
29. Method according to claim 27 wherein the boranocarbonate is Na<sub>2</sub>(H<sub>3</sub>BCO<sub>2</sub>).
30. Method according to any one of claims 18 to 29 wherein
- 15 the medicament further includes a guanylate cyclase stimulant or stabilizer.
31. Method according to claim 30 wherein the guanylate cyclase stimulant or stabilizer is a molecule or ion uncombined with the boranocarbonate compound or ion.
- 20 32. Method according to claim 30 or 31 wherein the guanylate cyclase stimulant or stabilizer is YC-1.
33. Method according to any one of claims 30 to 32 comprising simultaneous or sequential administration of the boranocarbonate compound or ion and the guanylate cyclase
- 25 stimulant or stabilizer.
34. Use according to any one of claims 18 to 33 wherein the boranocarbonate compound or ion is other than



I.  $K_2 (H_3BCOO)$



where R, R' = H, alkyl, perfluoroalkyl.

35. A method of treating a viable mammalian organ extracorporeally or an isolated mammalian organ, comprising contacting the organ with a pharmaceutical composition comprising a boranocarbonate compound or ion adapted to make CO available for physiological effect.

36. A method according to claim 35 wherein the boranocarbonate compound or ion is as defined in any one of claims 4 to 12.

37. Method according to 35 or 36 wherein the composition further includes a guanylate cyclase stimulant or stabilizer.

38. Method according to claim 37 wherein the guanylate cyclase stimulant or stabilizer is a molecule or ion uncombined with the boranocarbonate compound or ion.

39. Method according to claim 37 or 38 wherein the guanylate cyclase stimulant or stabilizer is YC-1.

40. A medical or veterinary implant carrying, in a form releasable at the implant site, a boranocarbonate compound or ion adapted to make CO available for physiological effect.

41. An implant according to claim 40 wherein the boranocarbonate compound or ion is as defined in any one of claims 4 to 12.

42. An implant according to 40 or 41 wherein the medicament further includes a guanylate cyclase stimulant or stabilizer.

43. An implant according to claim 42 wherein the guanylate cyclase stimulant or stabilizer is a molecule or ion uncombined with the boranocarbonate compound or ion.

44. An implant according to claim 42 or 43 wherein the guanylate cyclase stimulant or stabilizer is YC-1.

45. A method of introducing CO to a mammal as a therapeutic agent comprising:

- 5           a) administering a boranocarbonate which makes available CO suitable for physiological effect; and  
          b) administering a guanylate cyclase stimulant or stabiliser.

10           46. A method according to claim 45, which is for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent, or for the treatment of any of hypertension, radiation damage, endotoxic shock, inflammation, inflammatory-related diseases, hyperoxia-induced injury, apoptosis, cancer, transplant  
15           rejection, post-operative ileus, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction, adult respiratory distress syndrome, vascular restenosis, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative  
20           colitis or for treatment in balloon angioplasty, aortic transplantation or survival of a transplanted organ.

          47. A method according to claim 45, which is for the stimulation of neurotransmission, vasodilation or smooth muscle relaxation by CO as a physiologically effective agent,  
25           or for the treatment of any of acute or chronic systematic hypertension, radiation damage, endotoxic shock, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, post-operative ileus, arteriosclerosis, post-ischemic organ damage, angina, haemorrhagic shock, sepsis, penile erectile  
30           dysfunction, vascular restenosis, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis or for treatment in balloon angioplasty, aortic transplantation or survival of a transplanted organ.

          48. A method according to claim 45, which for the stimulation  
35           of neurotransmission, vasodilation or smooth muscle relaxation

by CO as a physiologically effective agent, or for the treatment of any of acute or chronic systematic hypertension, hyperoxia-induced injury, cancer by the pro-apoptotic effect of CO, transplant rejection, post-operative ileus, post-  
5 ischemic organ damage, angina, haemorrhagic shock, penile erectile dysfunction, hepatic cirrhosis, cardiac hypertrophy, heart failure and ulcerative colitis or for treatment in balloon angioplasty or aortic transplantation.

49. A method according to claim 45, which is for treatment of  
10 any of acute or chronic systemic hypertension, pulmonary hypertension, transplant rejection, post-operative ileus, arteriosclerosis, post-ischemic organ damage, myocardial infarction, penile erectile dysfunction, vascular restenosis, hepatic cirrhosis, cardiac hypertrophy, heart failure, chronic  
15 anal fissure, internal anal sphincter disease, anorectal disease, and ulcerative colitis or for treatment in balloon angioplasty or aortic transplantation.

50. A method according to any one of claims 45 to 49 wherein the boranocarbonate compound or ion is as defined in any one  
20 of claims 5 to 13.

51. A method according to any one of claim 45 to 50 wherein the guanylate cyclase stimulant or stabilizer is a molecule or  
ion uncombined with the boranocarbonate compound or ion.

52. A method according to any one of claims 45 to 51 wherein  
25 the guanylate cyclase stimulant or stabilizer is YC-1.

53. A pharmaceutical composition comprising:

a) a boranocarbonate compound or ion which makes available CO suitable for physiological effect; and

b) a guanylate cyclase stimulant or stabiliser.

30 54. A composition according to claim 53 wherein the boranocarbonate compound or ion is as defined in any one of claims 4 to 12.

55. A composition according to claim 53 or 54 wherein the  
35 guanylate cyclase stimulant or stabilizer is a molecule or ion uncombined with the boranocarbonate compound or ion.

56. A composition according to any one of claims 53 to 55 wherein the guanylate cyclase stimulant or stabilizer is YC-1.

57. A composition according to any one of claims 53 to 56, adapted for one of simultaneous and sequential administration  
5 of the boranocarbonate compound or ion and the guanylate cyclase stimulant or stabilizer.